Posttraumatic Stress Disorder: Etiology, Phenomenology, and Treatment

Edited by

Marion E. Wolf, M.D.
Chief, Tardive Dyskinesia Program
North Chicago V.A. Medical Center
North Chicago, Illinois; and
Clinical Professor of Psychiatry
Loyola University Stritch School of Medicine
Maywood, Illinois

Aron D. Mosnaim, Ph.D.
Professor of Pharmacology and Molecular Biology
University of Health Sciences/
The Chicago Medical School
North Chicago, Illinois

Washington, DC
London, England

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Chapter 16

Interrelationships Between Biological Mechanisms and Pharmacotherapy of Posttraumatic Stress Disorder

Matthew J. Friedman, M.D., Ph.D.

It is no longer controversial whether there are biologic alterations associated with posttraumatic stress disorder (PTSD). During the past 5 years, a growing body of research findings has shown that patients with PTSD exhibit abnormalities in sympathetic nervous system arousal, in hypothalamic-pituitary-adrenocortical (HPA) axis function, in the endogenous opioid system, and in the physiology of sleep and dreaming (Friedman 1988, in press; van der Kolk 1987). Psychopharmacologic approaches to PTSD have progressed at a slower pace. Results from the few controlled drug trials that have been published to date are contradictory with respect to the efficacy and specificity of the drugs under consideration.

In this overview, I will evaluate the current status of basic and clinical research on PTSD and will show that biologic approaches to the diagnosis and treatment of PTSD clearly complement more traditional psychological approaches. In addition, I will focus on the most common concurrent psychiatric diagnoses associated with PTSD to determine whether such clinical comorbidities can be understood in terms of the pathophysiology of PTSD. Specifically, I will address biologic issues pertinent to the co-occurrence of PTSD and comorbid diagnoses such as alcoholism, drug abuse and dependency, personality disorders, major depression, and panic disorder. I will also review the current status of psychopharmacologic research on PTSD with regard to antidepressants, antipanic/anxiolytics, carbamazepine, lithium, and neuroleptics.

Methodological Considerations

Before evaluating the current status of work in the field, it is useful to reflect on three methodological issues specifically pertinent to PTSD: 1) PTSD can be produced in the clinical laboratory; 2) there are animal models of PTSD; and 3) PTSD comorbidities raise important questions about the relationship between PTSD and frequently associated disorders.

PTSD in the Clinical Laboratory

The hallmark of PTSD is a conditioned emotional response to meaningful stimuli that evoke thoughts, memories, and feelings uniquely associated with the trauma itself (Kolb 1987). Therefore, subjects with PTSD can be provoked to recreate a full-blown PTSD episode in a controlled laboratory setting by exposure to traumagenic stimuli. In the case of combat veterans with PTSD, a variety of traumagenic stimuli have reliably produced psychophysiologic arousal states that clearly differentiate PTSD patients from

other groups of subjects. Traumagenic stimuli successfully employed in such experiments have included audiotapes of combat sounds (Blanchard et al. 1982), visual slides of Vietnam combat scenes (Malloy et al. 1983), videotape excerpts from the movie *Platoon* (Pitman et al. 1988), and autobiographical traumatic anecdotes read to the subject by the experimenter (Pitman et al. 1987). For this reason, it is methodologically possible to conduct A-B-A (off-on-off) experimental designs with PTSD patients in which various biologic (and psychological) parameters are monitored before, during, and after exposure to traumagenic stimuli. Such an approach should be the standard for laboratory biologic research on PTSD. Laboratory procedures for provoking and diagnosing PTSD are reviewed elsewhere (Friedman, in press).

Animal Models for PTSD

Van der Kolk et al. (1985) proposed that the animal model of learned helplessness to inescapable shock may be directly applicable to PTSD. Certainly the primacy of the Pavlovian paradigm, in which a conditioned stimulus becomes a sufficient condition for eliciting intense emotional arousal in experimental animals, suggests that this model may be much more applicable to PTSD than to affective disorders, as suggested by Siever and Davis (1985). Furthermore, the stimulus-driven behavior of PTSD can be explicated by classic psychological two-factor theory as originally proposed for traumatic avoidance learning in dogs by Solomon and Wynne (1954) and later extrapolated to traumatized war zone veterans by Keane et al. (1985). A recent comparison of inescapable versus escapable shock in rats suggests that the effect of the former condition is much more disruptive to learning through impairment of the hippocampal neural plasticity (Shores et al. 1989). Finally, van der Kolk (1987) and Friedman (1988) have independently hypothesized that chronic central sympathetic arousal in PTSD kindles limbic nuclei, thereby producing a stable neurobiologic abnormality. In other words, there is a wealth of psychological and neurobiologic theory and data that may be directly applicable to our understanding of PTSD. Furthermore, there are a number of well-developed animal research paradigms available for testing current clinical controversies about this disorder. Theoretical and animal models for PTSD are reviewed elsewhere (Kolb 1988; van der Kolk 1988).

PTSD Comorbidities

Other DSM-III-R (American Psychiatric Association 1987) psychiatric disorders are so frequently associated with PTSD that some have questioned whether PTSD itself is merely an artifact of observer bias (Behar 1987; Breslau and Davis 1987). Indeed, an epidemiologic survey of 2,348 Vietnam

veterans (Kulka et al. 1988) demonstrated that 50% of veterans with a current diagnosis of PTSD had at least one other psychiatric disorder that met DSM-III (American Psychiatric Association 1980) criteria. Furthermore, within a self-selected Veterans Administration cohort of 107,107 patients seeking mental health treatment, at least one other diagnosis was reported in 80% of patients with PTSD (Friedman et al. 1987). Among the most frequent comorbid diagnoses are alcoholism, substance abuse or dependency, personality disorders, major depressive disorder (MDD), and panic disorder.

Such findings have obvious implications for research and treatment. First, since uncomplicated PTSD is such a rarity in clinical settings, any useful investigations must control for the likely co-occurrence of these other psychiatric disorders. Second, we must ask whether the co-occurrence of PTSD and, for example, MDD alters the biological expression of one or both disorders so that associated biological alterations indicate neither PTSD nor MDD but rather a hybrid of the two disorders. Finally, the clinical reality of comorbidities must be factored into psychopharmacological research on PTSD.

With this as a frame of reference, I will now review the relationship between PTSD and the most frequent comorbid diagnoses with respect to our emerging understanding of the pathophysiology of PTSD and possible implications for diagnosis and treatment.

PTSD and Chemical Abuse and Dependency

Published reports indicate that among clinical treatment-seeking cohorts, 60% to 80% of PTSD patients have concurrent diagnoses of alcohol or drug abuse or dependency (Branchey et al. 1984; Keane et al. 1988). An epidemiologic survey of Vietnam veterans reported that, among individuals currently suffering from PTSD, current and lifetime prevalence rates for alcoholism were 23% and 75%, respectively, and current and lifetime drug abuse or dependency rates were 6% and 23%, respectively (Kulka et al. 1988). Furthermore, Vietnam veterans with higher levels of war zone stress are more likely to exhibit chemical abuse or dependency than those who experienced considerably less combat exposure (Keane et al. 1988; Kulka et al. 1988). This latter finding suggests that neurobiological alterations associated with PTSD may make affected individuals more susceptible to alcohol and substance abuse or dependency.

Since patients with PTSD exhibit sympathetic hyperarousal both at baseline and especially following exposure to traumagenic stimuli (Friedman 1988; Kolb 1987; Pitman et al. 1988), it follows that any drug that can suppress adrenergic activity will produce temporary relief from PTSD intrusion and arousal symptoms. Therefore, self-medication with sedating drugs such as ethanol, marijuana, central depressants, or opiates should not be an

unexpected behavioral consequence of PTSD. Furthermore, PTSD is associated with dysregulation of the endogenous opioid system, marked by lowered pain thresholds at rest and by stress-induced analgesia following exposure to traumagenic stimuli (Friedman, in press; Perry et al. 1987; Pitman et al. 1988). This suggests that PTSD patients may be biologically predisposed to reverse a chronic baseline endogenous opioid deficiency through self-medication with heroin, methadone, and other opiates.

In an elegant review of the biological basis for the comorbid occurrence of PTSD and chemical abuse or dependency, Kosten and Krystal (1988), invoking van der Kolk et al.'s (1985) inescapable shock model of PTSD, argued that the adrenergic arousal associated either with alcohol or opiate withdrawal will, itself, trigger a conditioned emotional response associated with PTSD symptoms during the vicious addiction-withdrawal cycle. They stated that the generic difficulties of treating any chemical dependency are amplified by the complex risk of exacerbating PTSD symptoms. It would appear, from this argument, that PTSD patients who are opiate addicts will be even more resistant to detoxification and rehabilitation than alcoholics, since the former addiction may reverse a chronic opioid deficiency associated with PTSD.

A final prediction from this hypothetical analysis is that PTSD patients will be less likely to self-medicate with cocaine, amphetamines, or other stimulants because such drugs will trigger sympathetic hyperarousal and thereby exacerbate PTSD intrusion and arousal symptoms. In my own clinical experience, PTSD patients tend to avoid central stimulants; this matter, however, has yet to be explored systematically.

To summarize, it is hypothesized that PTSD patients are especially susceptible to alcohol, marijuana, opiate, and central depressant abuse or dependency because of the biological abnormalities associated with their illness. This suggests that there may be a biologic basis for considering self-medication with such drugs a bona fide avoidant symptom of PTSD as originally proposed in DSM-III. With regard to treatment, it is clear that when PTSD and chemical abuse or dependency occur simultaneously, they must be treated simultaneously.

PTSD AND PERSONALITY DISORDERS

Among clinical treatment-seeking veteran cohorts, the co-occurrence of personality disorders with PTSD generally ranges between 40% and 60% (Boman 1986; Escobar et al. 1983; McFarland 1985; Sierles et al. 1983, 1986). Epidemiologic findings from the National Vietnam Veterans Readjustment Study showed a 20% lifetime prevalence rate of personality disorders among veterans who met DSM-III diagnostic criteria for PTSD (Kulka et al. 1988).

Lacking systematic, and especially longitudinal, studies on this matter, several issues come to mind that may be relevant to the biology of PTSD. First, presence of a personality disorder may predispose traumatized individuals to develop PTSD subsequently. Among the few studies on risk factors for PTSD, there is one report on traumatized Australian fire fighters showing higher neuroticism scores and greater prevalence of a personal history of psychiatric illness among individuals who later developed PTSD (McFarlane 1988). Other studies, however, show no such association (Friedman 1989).

Second, recent research on borderline personality disorder indicates that patients who carry this diagnosis have a high likelihood of having been physically and/or sexually traumatized during childhood (Herman et al. 1989; Zanarini et al. 1989). These data strongly suggest that patients with borderline personality disorder exposed to catastrophic stress during adulthood are actually being re-traumatized. If there are biologic alterations associated with borderline personality disorder and if they are similar to the abnormalities of PTSD, it follows that patients with borderline personality disorder may be especially vulnerable to developing PTSD following traumatic exposure.

Third, Cloninger (1987b) developed a systematic method for clinical description and classification of normal and abnormal personality variants in which he postulated an underlying genetic and neurobiological basis for the different personality disorders. Specifically, he proposed a tridimensional theory defined in terms of the basic stimulus-response characteristics of novelty seeking (dopaminergic), harm avoidance (serotonergic), and reward dependence (adrenergic). Some of his predictions regarding impulsivity, disinhibition, hostility, and type II alcoholism (Cloninger 1987a, 1987b) have been confirmed in patients with reduced central nervous system serotonergic function (Linnoila 1983, 1989). Such an approach obviously permits concurrent systematic investigation of PTSD and the various personality disorders to determine whether there is any overlap in observed biological abnormalities and whether such abnormalities in specific personality disorders might increase the risk for developing PTSD in traumatized individuals. In other words, such an approach provides a theoretical tool for understanding the high clinical comorbidity between PTSD and personality disorders.

PTSD AND MDD

Outpatient clinical cohorts show lifetime prevalence rates of MDD among PTSD patients ranging from 26% to 65% (Boman 1986; Escobar et al. 1983; Friedman et al. 1987; McFarland 1985). Epidemiologic data show that among Vietnam veterans with current PTSD, 20% meet DSM-III criteria for lifetime MDD (Kulka et al. 1988).

Table 16-1 shows that PTSD and MDD have many symptoms in com-

Table 16-1. Posttraumatic stress disorder and major depressive disorder: similarities

Dysphoria	Social withdrawal
Guilt	Insomnia
Grief	Decreased delta sleep
Anhedonia	Respond to tricyclic antidepressants
Irritability	Respond to monoamine oxidase inhibitors

mon. Indeed, one recent study's finding that 46% of hospitalized PTSD patients met DSM-III criteria for MDD (Reaves et al. 1989) is representative of other clinical reports. From the nosologic perspective of DSM-III-R, the major depression associated with PTSD is indistinguishable from the MDD observed in patients without PTSD. This is true both with regard to clinical symptomatology and with regard to responsivity to tricyclic antidepressants (TCAs) and to monoamine oxidase inhibitors (MAOIs). However, as will be shown below, this comparable psychopharmacologic responsivity may be more apparent than real.

As shown in Table 16-2, however, PTSD and MDD have a number of significant differences that can be detected using biological techniques. Psychophysiologic arousal provoked by exposure to traumagenic stimuli is the hallmark of PTSD and is unique to this disorder (Blanchard et al. 1982; Brende 1982; Dobbs and Wilson 1961; Gillespie 1942; Malloy et al. 1983; Pitman et al. 1987). Such traumagenic stimuli can produce a naloxone-reversible stress-induced analgesia in PTSD but not in MDD (Pitman et al. 1988, 1989). PTSD patients exhibit abnormally low beta-adrenergic binding in both intact lymphocytes and platelet membrane preparations as well as significant reductions in beta-adrenergic receptor-mediated cyclic adenosine monophosphate signal transduction (Lerer et al. 1987a), in contrast to depressed patients who characteristically exhibit up-regulation of beta-adrenergic receptors (Sulser et al. 1978). HPA function is reduced in PTSD and is excessive in depression as measured by the dexamethasone suppression test (DST), 24-hour urinary free cortisol levels, or serum cortisol levels (Halbreich et al. 1988; Kudler et al. 1987; Mason et al. 1986). Sleep research suggests that the sleep architecture in PTSD shows a different pattern of abnormalities than in MDD. Specifically, depressed patients exhibit reduced rapid eye movement (REM) latency, reduced delta sleep, and prolongation of the first REM period (Akiskal 1983; Dube et al. 1986; Kupfer and Thase 1983; Ross et al. 1990). On the other hand, most research to date suggests that PTSD patients exhibit excessive Stage 1 and Stage 2 sleep, reduced delta, reduced REM percentage, and increased REM latency (Friedman 1988; Kramer and Kinney 1985; Lavie et al. 1979; Schlossberg and Benjamin 1978). It should be noted, however, that some sleep researchers have observed sleep electroencephalogram findings in PTSD patients that look

Table 16-2. Posttraumatic stress disorder and major depressive disorder: differences

Posttraumatic stress disorder	Major depressive disorder
Stimulus-driven behavior	Not stimulus driven
Stress-induced analgesia	No stress-induced analgesia
Down-regulated beta-receptors	Up-regulated beta-receptors
HPA axis hypofunction	HPA axis hyperfunction
DST suppression	DST nonsuppression
Increased Stage 1 and Stage 2 sleep	Normal Stage 1 and Stage 2 sleep
Possible increased REM latency	Decreased REM latency
Probable decreased total REM period duration	Increased length first REM period
Responds to propranolol	Worsened by propranolol
Responds to carbamazepine	No response to carbamazepine
Responds to benzodiazepines	Worsened by benzodiazepines

Note: HPA = hypothalamic-pituitary-adrenal; DST = dexamethasone suppression test; REM = rapid eye movement.

much more like typical results in MDD (Greenberg et al. 1972; Kauffman et al. 1987; van Kammen et al. 1987). Finally, drug trials suggest that medications that ameliorate PTSD symptoms, such as propranolol, benzodiazepines, and carbamazepine, either exacerbate depressive symptoms or are without effect in MDD. (These pharmacologic results will be addressed in detail below.)

Given the differences between PTSD and MDD shown in Table 16-2, it would appear that the two disorders can be distinguished through a number of provocative diagnostic tests. For example, PTSD appears to be associated with HPA axis hypofunction, whereas MDD is characterized by HPA axis hyperfunction. Indeed, the work of Kudler et al. (1987) with the DST is consistent with this expectation, since PTSD patients exhibited DST suppression, whereas patients with both PTSD *and* MDD showed DST nonsuppression. This experiment also suggests that when PTSD and MDD occur concurrently, the biological abnormalities associated with MDD predominate over those associated with PTSD, hence DST nonsuppression. On the other hand, Halbreich et al. (1988) reached the opposite conclusion when they compared DST responses in patients with MDD alone versus a group of PTSD patients with MDD. As expected, the MDD patients were DST nonsuppressors, but, in contrast to Kudler et al.'s results, the PTSD patients with MDD were DST *suppressors*. Hence Halbreich et al. concluded that when PTSD and MDD occur concurrently, the biological abnormalities associated with PTSD predominate over those associated with MDD.

There are several tentative conclusions from these two studies. First, the DST may not be useful for distinguishing PTSD from MDD. Second, when

PTSD and MDD occur simultaneously, each may alter the biological expression of the other. Third, some MDD associated with PTSD may be qualitatively (biologically) distinct from true melancholia even though both meet DSM-III-R criteria for MDD. Perhaps it will be biologically meaningful to revive the distinction between primary and secondary depression in this regard. Primary depression (true melancholia) associated with PTSD is marked by HPA axis hyperfunction with DST nonsuppression and by characteristic depressive alterations in REM sleep. Secondary depression is actually a clinical manifestation of PTSD itself, rather than a separate disorder. It is characterized by normal-to-reduced HPA axis activity, with DST suppression, and by marked abnormalities in Stage 1 and Stage 2 sleep. Since the DSM-III-R cannot distinguish between primary and secondary depression, it may be necessary to utilize biological probes such as the DST and sleep electroencephalogram to categorize the associated depressive syndrome accurately. Finally, when MDD occurs in conjunction with PTSD, determining whether such depression is primary or secondary may explain discrepant psychopharmacological results with antidepressant medications.

ANTIDEPRESSANTS AND PTSD

Tricyclic Antidepressants

There is a general consensus that antidepressants help patients with PTSD. Open and controlled trials with TCAs and MAOIs have generally reported some sort of symptom relief. The question in evaluating this research is whether these drugs have a specific efficacy for PTSD symptoms rather than for depressive symptomatology. A number of open-drug studies have reported that TCAs effectively reduce DSM-III-R PTSD intrusive recollections and hyperarousal symptoms but have little effect on avoidant symptomatology (Blake 1986; Boehnlein et al. 1985; Burstein 1982; Embry and Callahan 1988; Falcon et al. 1985; Friedman 1981, 1988; Marshall 1975; Reaves et al. 1989; van der Kolk 1987). There is less unanimity, however, when one considers the three completed double-blind trials of TCAs in patients with PTSD.

Frank et al. (1988) performed a double-blind evaluation of imipramine, phenelzine, and placebo in 34 Vietnam combat veterans with PTSD. In their study, both the TCA and MAOI appeared to have a specific action against PTSD symptoms, since patients in both drug groups showed significant reduction in intrusion (but not avoidance) items, as measured by the Impact of Event Scale (Horowitz et al. 1979). Therapeutic efficacy of imipramine and phenelzine appeared to be specific for PTSD, since patients showed no significant improvement in depressive or anxious symptoms. It is important

to note that no subjects in this study met DSM-III-R criteria for major depression.

Results from two other groups have contradicted these findings. Double-blind, placebo-controlled comparisons of amitriptyline (Davidson et al. 1988) and desipramine (Reist et al. 1989) have shown no improvement in PTSD symptoms. The only therapeutic effects of these TCAs were on depressive symptoms of subjects in both studies. There is an important sampling difference between these studies that may have affected the results. Whereas Frank et al. (1988) excluded all major depressive patients from their study, both Davidson et al. and Reist et al. included many patients with MDD. We will return to this point later.

Monoamine Oxidase Inhibitors

With regard to MAOIs, a number of open studies have also demonstrated that phenelzine is efficacious against intrusive (but not avoidant) symptoms as well as against depressive and generalized anxiety symptoms (Davidson et al. 1987; Hogben and Cornfield 1981; Lerer et al. 1987b; Milanes et al. 1984; Shen and Park 1983). In the comparison of imipramine, phenelzine, and placebo mentioned above, Frank et al. (1988) found that phenelzine was even more effective than imipramine against intrusive (but not avoidant) symptoms. On the other hand, in a double-blind, crossover comparison, Shestatzky et al. (1988) found no superiority of phenelzine over placebo.

Summary

Current research with TCAs and MAOIs is inconclusive with regard to efficacy of antidepressants against the specific symptoms of PTSD. Both drugs remain effective against depressive symptoms in patients with PTSD and MDD. Is this because TCAs and MAOIs are only marginally effective in PTSD? Or do these results suggest that the mechanism of action for antidepressants is primarily through an antipanic/anxiolytic effect that is obscured when MDD is present? These are obviously empirical questions that must await the accumulation of an adequate number of controlled studies before they can be answered with conviction. Sample sizes are small in the few double-blind trials conducted to date. On the other hand, these ambiguous research results with TCAs and MAOIs suggest other questions about the relationship between PTSD and depressive symptoms. Specifically, we must ask whether the difference between Frank et al.'s (1988) results in comparison with those of both Davidson et al. (1988) and Reist et al. (1989) has something to do with the fact that patients with MDD were excluded from the former study but included in relatively large numbers in the latter two studies.

PTSD AND PANIC DISORDER

Although the prevalence of panic disorder in a Veterans Administration outpatient treatment-seeking cohort of more than 100,000 veterans was only 1.2%, 21% of all veterans with panic disorder also met DSM-III criteria for PTSD (Friedman et al. 1987). This high comorbidity rate reflects the great symptomatic similarity between these two disorders and raises the question of overlapping pathophysiologic abnormalities.

Table 16-3 shows similarities between PTSD and panic disorder. Mellman and Davis (1985) have suggested that PTSD flashbacks actually meet DSM-III-R diagnostic criteria for panic attacks. Such an assertion, however, may actually obscure the important differences between the two disorders, listed in Table 16-4. PTSD episodes are psychological events driven by meaningful traumagenic stimuli that evoke stress-induced analgesia (Pitman et al. 1988) along with a sympathetic storm. Panic disorder, on the other hand, is marked by spontaneous physiological attacks devoid of psychological meaning in which stress-induced analgesia has not been demonstrated. Sodium lactate infusions can definitely precipitate panic attacks (Pitts and McClure 1967), but lactate has produced very ambiguous PTSD "flashbacks" in the only reported study on this matter (Rainey et al. 1987). Vietnam combat veterans who met DSM-III criteria for *both* PTSD and panic disorder responded to lactate infusion with "flashbacks" pertinent to a hospital setting or to the experimental laboratory rather than to the combat trauma that precipitated their PTSD. Sleep architecture (Hauri et al. 1989) is normal in panic disorder, whereas PTSD patients show a disturbance of the sleep architecture marked by increased Stage 1 and Stage 2 sleep, decreased delta sleep, increased REM latency, and probable reduction in total REM duration. HPA axis activity is apparently normal in panic disorder but diminished in PTSD. Finally, patients with panic disorder do not respond to carbamazepine (Uhde et al. 1988), whereas open trials with this drug in PTSD patients have been quite promising (Lipper et al. 1986; Wolf et al. 1988).

A number of questions remain. Can sodium lactate infusions precipitate bona fide PTSD episodes? If so, can they reliably distinguish panic disorder

Table 16-3. Posttraumatic stress disorder and panic disorder: similarities

Sympathetic hyperarousal	Often associated with major depressive disorder
Sudden surges of anxiety	
Flashbacks and panic attacks	Postulated locus coeruleus dysregulation
Increased sleep latency	Respond to tricyclic antidepressants
Decreased sleep efficiency	Respond to monoamine oxidase inhibitors
Increased movement during sleep	Respond to propranolol and clonidine

from PTSD? When panic disorder and PTSD occur simultaneously, will each alter the biological expression of the other? Is the panic disorder that occurs concurrently with PTSD qualitatively distinct from true panic disorder, even though both meet DSM-III-R criteria for the same disorder?

Antipanic and Anxiolytic Agents and PTSD

Medications efficacious in PTSD include sympatholytic drugs such as propranolol and clonidine in addition to TCAs and MAOIs. With one exception, all reports on clonidine, propranolol, benzodiazepines, and alprazolam have been descriptions of open-drug trials.

Propranolol

In the only controlled drug trial published to date, propranolol in doses up to 2.5 mg/kg/day was tested in 11 children with acute PTSD who had been physically and/or sexually abused. The study was an A-B-A design (off-on-off medication) in which patients exhibited significantly fewer symptoms during active treatment (Famularo et al. 1988). In an open propranolol trial with combat veterans with chronic PTSD who received 120 to 160 mg daily, Kolb et al. (1984) reported marked reductions in nightmares, intrusive recollections, hypervigilance, insomnia, startle responses, and angry outbursts. On the other hand, Kinzie (1989) reported that beta-blockers have been without effect on PTSD symptoms of traumatized Cambodian refugees. Given the high ratio of chemical abuse and dependency observed in PTSD patients (Branchey et al. 1984; Keane et al. 1988), the low abuse

Table 16-4. Posttraumatic stress disorder and panic disorder: differences

Posttraumatic stress disorder	Panic disorder
Attacks stimulus-driven	Attacks spontaneous
Attacks psychological	Attacks physiologic
Stress-induced analgesia	No stress-induced analgesia
Role of lactate unclear	Precipitated by lactate
HPA axis hypofunction	Normal HPA axis function
Increased Stage 1 and Stage 2 sleep	Normal Stage 1 and Stage 2 sleep
Decreased delta sleep	Normal delta
Possible increased REM latency	Normal REM latency
Probable decreased total REM duration	Normal REM duration
Responds to carbamazepine	No response to carbamazepine

Note: HPA = hypothalamic-pituitary-adrenal; REM = rapid eye movement.

potential of beta-blockers will make such drugs an attractive treatment option if their efficacy can be demonstrated conclusively.

Clonidine

There are two favorable reports on open trials with the alpha$_2$ agonist clonidine. From a theoretical standpoint, clonidine is an interesting agent to consider, since it will reduce the postulated central adrenergic arousal through inhibition of the locus coeruleus. Furthermore, clonidine would be expected to neutralize the opiate withdrawal-like symptoms of PTSD postulated by van der Kolk et al. (1985) in their inescapable shock model of PTSD. Kolb et al. (1984) reported that eight combat veterans experienced improved sleep, fewer nightmares, lessened explosiveness, reduced intrusion symptoms, and lessened hyperalertness following an open trial of clonidine 0.2 to 0.4 mg/day. Kinzie (1989) observed marked reductions in anxiety and autonomic arousal among Cambodian refugees with PTSD treated with clonidine. Results were even better when clonidine was combined with TCAs.

Benzodiazepines

In a report from one Veterans Administration hospital, 71% of PTSD patients received benzodiazepines either exclusively (36%) or in combination with other drugs (Ciccone et al. 1988). Certainly the proven anxiolytic potency of these drugs has led to their wide use despite clinical concerns about addiction as well as the complete absence of any controlled studies demonstrating their efficacy in PTSD. From a theoretical point of view, the kindling model of PTSD offers a neurobiological argument for prescribing benzodiazepines for appropriate patients. Since limbic kindling is associated with increased benzodiazepine receptor binding (McNamara et al. 1985; Morita et al. 1985; Tietz et al. 1985), it follows that benzodiazepines and other gamma-aminobutyric acid (GABA) agonists or synergists might be particularly useful in well-selected PTSD patients.

Alprazolam

Alprazolam shares the general properties of most benzodiazepines along with antipanic and possible antidepressant actions (Feighner et al. 1983; Sheehan 1982). Like other benzodiazepines, it has been widely prescribed for PTSD patients despite a complete lack of published double-blind trials demonstrating its efficacy. Alprazolam's short half-life raises, in addition to generic concerns about addiction, the possibility of clinical complications such as rebound anxiety and withdrawal symptoms (Higgitt et al. 1985; Noyes et al. 1985).

Summary

Current research with antipanic and anxiolytic agents is very sparse. There is only one controlled study with propranolol and a very low number of published open trials with beta-blockers, clonidine, benzodiazepines, or alprazolam.

Other Drugs and PTSD

Carbamazepine

Carbamazepine is particularly interesting from a theoretical point of view. It was introduced by Lipper et al. (1986) because it is an anticonvulsant that effectively counters the neurobiological changes produced by kindling. Van der Kolk (1987) and Friedman (1988) have independently hypothesized that the chronic central nervous system sympathetic arousal associated with PTSD produces an endogenous state in the brain that optimizes the conditions for limbic kindling. Therefore, the efficacy of carbamazepine in two open trials with PTSD patients is consistent with a kindling model of PTSD (Lipper et al. 1986; Wolf et al. 1988). Lipper et al. reported reduced intrusive symptoms such as traumatic nightmares, flashbacks, and intrusive recollections in 7 of 10 combat veterans with chronic PTSD. Wolf et al. reported alleviation of impulsivity, irritability, and violent behavior in 8 of 10 combat veterans with PTSD. Wolf et al. did not specifically report on PTSD symptoms, and their positive results could be due to carbamazepine's attentuation of anger and rage rather than on a specific improvement in PTSD. On the other hand, the fact that all of their patients had normal electroencephalograms and had no evidence of temporal lobe epilepsy suggests that their patients did not have complex partial seizures that had been misdiagnosed as PTSD (Stewart and Bartucci 1986). Obviously, there is a need for double-blind trials with carbamazepine in future research.

Lithium

According to van der Kolk (1987), the therapeutic response to lithium is indistinguishable from that to carbamazepine. Of 22 patients with PTSD treated with lithium, 14 reported reduced sympathetic arousal, better tolerance to stress, and diminished alcohol intake. Of note are clinical reports that lithium is an effective treatment for PTSD patients without a personal or family history of affective illness (Kitchner and Greenstein 1985; van der Kolk 1983). Again, controlled trials are needed to validate these open trials and clinical anecdotes.

Fluoxetine

Should lithium stand the test of double-blind trials, it would raise pertinent theoretical questions about the serotonergic system in PTSD. This possibility has not been investigated systematically. However, the impulsivity, disinhibition, hostility, and alcohol (and other chemical) abuse or dependency often associated with PTSD point to the serotonergic system as potentially important (Branchey et al. 1984; Carol et al. 1985; Cloninger 1987a; Hyer et al. 1986; Jelinek and Williams 1984; Keane et al. 1988; Penk et al. 1981; Yager 1976; Yager et al. 1984). Such questions would provide a useful theoretical context in which to evaluate vigorously serotonin reuptake inhibitors (e.g., fluoxetine) that are currently achieving anecdotal success in certain centers.

Neuroleptics

Psychiatrists have become much more reluctant to prescribe neuroleptics than they were 20 years ago. At that time, unrecognized PTSD appeared to be a bizarre and explosive psychotic disorder marked by agitation, paranoid thoughts, loss of control, potential for violence, and brief psychotic episodes now called flashbacks. Clinical observations that, in most cases, these symptoms could be controlled by antidepressants or antipanic and anxiolytic agents have relegated neuroleptics to second- or third-line drugs. Although neuroleptics have no place in the routine treatment, they do have a place in the treatment of refractory PTSD marked by paranoid behavior, aggressive psychotic symptoms, uncontrollable anger, self-destructive behavior, and frequent flashback episodes marked by frank auditory and visual hallucinations of traumatic episodes (Friedman, in press; Mueser and Butler 1987; Walker 1982). Neuroleptics should never be prescribed until other agents have been tried. As with other drugs mentioned above, there have been no controlled trials in PTSD with neuroleptic agents.

SUMMARY

In this review, I have focused on biological aspects of the clinical treatment of PTSD. My starting point was current evidence that PTSD is associated with sympathetic nervous system hyperarousal, HPA axis hypofunction, endogenous opioid dysregulation, and abnormalities in the physiology of sleep. I accept the robust finding that PTSD is usually associated with other psychiatric disorders and question whether such clinical comorbidities can be understood in terms of the pathophysiology of PTSD.

Chemical abuse and dependency can readily be understood as a maladaptive coping strategy to neutralize the sympathetic hyperarousal and opioid dysregulation associated with PTSD. It follows that when PTSD and

chemical abuse or dependency occur simultaneously, they must be treated simultaneously.

Certain types of personality disorders may eventually be shown to share some of the biological abnormalities seen in PTSD and thereby predispose affected individuals to develop PTSD following traumatic exposure.

Major depressive disorder is reviewed with respect to characteristics by which it both resembles and differs from PTSD. Data on HPA axis function and sleep physiology are cited to illustrate the unique patterns of biological abnormalities seen in MDD and PTSD, respectively. Despite such differences, use of biological tests to distinguish MDD from PTSD may have limited value, since it appears that when both disorders occur simultaneously, each may alter the biological expression of the other. Such findings raise the possibility that, in some cases, MDD associated with PTSD may be qualitatively (biologically) distinct from true melancholia even though both meet DSM-III-R criteria for MDD. Finally, current research on the specificity and efficacy of antidepressants (TCAs and MAOIs) in PTSD is reviewed. Although there are many published positive reports on the efficacy of TCAs and MAOIs in PTSD, results from controlled trials are inconclusive at this time.

Panic disorder is reviewed with respect to characteristics by which it both resembles and differs from PTSD. There is much less research on PTSD's relationship to panic disorder than the aforementioned studies on PTSD and MDD. The one study on sodium lactate infusion in PTSD is ambiguous. Clinical psychopharmacological studies on antipanic and anxiolytic agents are reviewed, with specific mention of propranolol, clonidine, benzodiazepines, and alprazolam. As with the literature on antidepressants, most positive reports are based on open trials or case reports.

Other drugs reviewed in the final section include carbamazepine, lithium, fluoxetine, and neuroleptics. Since none of these drugs have been tested in controlled trials, I focused the discussion on theoretical and practical issues rather than scientific data.

In conclusion, it appears that the high co-occurrence of other psychiatric disorders in conjunction with PTSD tells us something very important about PTSD itself. From a theoretical point of view, overlapping biological abnormalities between PTSD and some comorbid diagnoses suggest that PTSD patients may be particularly susceptible to develop certain other psychiatric disorders. Thus, the clinical reality of comorbidities must be factored into all of our treatment approaches to PTSD.

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